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TITLE: **A Novel Association and Therapeutic Targeting of Neuropilin-1 and MUC1 in Pancreatic Cancer**

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14. ABSTRACT

We hypothesized that MUC1, a transmembrane glycoprotein that is overexpressed in >80% of pancreatic ductal adenocarcinoma induces a pro-angiogenic tumor microenvironment by increasing the level of NRP1 and VEGF thereby enhancing angiogenesis and metastasis. We report that MUC1hi PC cells and tumors in vitro and in vivo not only express higher levels of NRP1 but also express higher levels of VEGFR2 and its phosphorylation forms as well as secrete higher levels of VEGF than MUC1low PC cells. This enables the MUC1hi/NRP1hi cells to induce endothelial cell tube formation and generate long ectopic blood vessels and enhanced distant metastasis. In the proposal, we also hypothesized that blocking the interaction between VEGF165 and NRP1 within the tumor microenvironment will lead to therapeutic benefit. Indeed, in vivo blocking NRP1 significantly reduces tumor burden in the MUC1hi mouse and human tumors. For the in vivo MUC1-specific tumor targeting, we demonstrate that our antibody TAB004 binds MUC+ve tumors in vitro and in vivo by section staining or live animal imaging. Thus, we conclude that NRP1 may be a promising target for MUC1hi PC and in the future conjugating to the MUC1 antibody for targeted delivery may enhance its potency.

15. SUBJECT TERMS
Neuropilin-1, MUC1, VEGF, Angiogenesis, Pancreatic Cancer

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Table of Contents

Page

Introduction:

Pancreatic cancer (PC) is a lethal disease. We hypothesize that MUC1 induces a pro-angiogenic tumor microenvironment by increasing the level of NRP1, thus enhancing angiogenesis, disease progression and metastases. Second, blocking the interaction between $VEGF_{165}$ and NRP1 within the tumor microenvironment will lead to therapeutic benefit. We report progress for all three tasks that we had proposed. I have thus broken the report down by tasks. The objective and specific aims are stated below. This is followed by the individual tasks with the progress made for that task. We show 15 figures in total. Figures 1-7 are for Task 1, Figures 8-10 are for Task 2, and Figures 11-15 are for Task 3.

Objectives/Specific Aims:

To test the effects of MUC1+ve PC cells on *in vitro* endothelial cell function in a NPR1-dependent fashion.

To determine if MUC1 up-regulates NRP1 and creates a pro-angiogenic niche *in vivo.*

To directly target angiogenesis within the tumor microenvironment by using TAB 004 MUC1 antibody conjugated to a peptide blocking VEGF-NPR1 binding.

Keywords
Neuropilin-1, MUC1, VEGF, Angiogenesis, Pancreatic Cancer

Overall Project Summary

Task 1:

To test the effects of MUC1+ PC cells on *in vitro* endothelial cell function in an NRP1-dependent fashion (0-9 months). For this task we perform *in vitro* angiogenesis assays to assess the ability of MUC1-expressing pancreatic cells to enhance endothelial cell proliferation, invasion and tube formation via NRP1.

Thus, we first determined if a correlation exists between MUC1 and NRP1 in a panel of human PDA cell lines that endogenously express high or low MUC1. Next we determined if MUC1 regulates NRP1 expression by conducting gain of function (stably transfected full length MUC1 in MUC1-low cells) and loss of function studies (by knocking down MUC1 using MUC1 specific siRNA). Figure 1A clearly shows that cells expressing high endogenous MUC1 also have high NRP1 while cells with low endogenous MUC1 has low NRP1 with exception (Panc1). We show that overexpressing full length MUC1 in two separate MUC1low cell lines (BxPC3 and Panc02) can induce higher expression of NRP1 (Figure 1B) while knocking down MUC1 from three other MUC1hi cell lines (HPAC, CFPAC and HPAFII) can reduce NRP1 expression. Whether this regulation is direct or indirect is not yet delineated.

We have established two mouse PDA cell lines, i.e. KC and KCKO, from spontaneously arising PDA tumors in WT (Muc1 intact) versus in Muc1 null mice [1]. A gene microarray was conducted in those two cells. Among those selected genes, KC cells showed higher NRP1 and NRP2 levels (Figure 2). Different from NRP2, NRP1 is mainly expressed on vascular endothelial cells and involved in the VEGF-induced angiogenesis. To validate the NRP1 expression data obtained from gene microarray, we further confirmed the expression of Muc1 in KC cells by flow cytometry (Figure 3A, left panel), and found KC cells displayed moderately higher NRP1 on their surface than KCKO cells (Figure 3A, right panel). Data from Western blotting showed consistent

results (Figure 3B). To further elucidate the mechanism, we determined the other VEGF receptor levels in these cells. This is especially important as NRP1 is only a co-receptor of VEGF and signaling through VEGFR2 is critical for the angiogenic signaling to occur [2]. We show that KCKO (Muc1 null) cells have moderately lower levels of VEGF receptor 1, 2, and 3 than its counterpart KC cells which have an intact Muc1 (VEGFR2 in Figure 3B, and data not shown).

Then, to elucidate the role of higher levels of NRP1 and VEGFR2 in KC cells, we compared the cell response to VEGF stimulation. Due to the difficulty of detecting phosphorylation of VEGFR2 *in vitro* (data not shown), Erk activation was evaluated instead which is downstream of VEGFR2 activation. There was higher level of endogenous Erk phosphorylation in KC cells (Figure 4A), and 60 min after stimulation with VEGF there was an increase of p-Erk in KC cells but not in KCKO cells. Erk is involved in many aspects in response to VEGF, including proliferation, survival, EMT, and angiogenesis. Thus, the cell proliferation was compared between KC and KCKO cells. It showed in Figure 4B, both cells proliferated similarly (left panel). VEGF did not promote cell proliferation, and blocking NRP1 function by its antagonist peptide A7R did not prevent KC cells from proliferation (right panel), which suggested that VEGF signaling was not required for KC or KCKO cell proliferation. However, the survival of Muc1-bearing KC cells was largely better than Muc1-null KCKO cells in response to serum starvation (Figure 4C). Whether the poor survival of KCKO cells is due to Muc1 deficiency or lower level of Muc1-associated VEGFR2 signaling will be clarified. Additionally, we observed that the Muc1/MUC1-bearing KC or BxPC3 cells migrated slightly better than their counterparts in the scratch assay (Figure 5).

Furthermore, KC cells secreted significantly higher level of VEGF than KCKO cells (Figure 6A), which could be partially inhibited by A7R (Figure 6C) without clearly affecting cell numbers (Figure 6B). These data suggest that VEGF secreted by tumor cells can positively feedback themselves through the NRP1-VEGFR2 signaling.

Lastly, we studied whether the supernatants from KC and KCKO cell cultures can differentially regulate the NRP1 level and its associated function in murine endothelial cells, 2H11. As shown in Figure 7A, 2H11 cells endogenously expressed high levels of NPR1 (left and middle panels), which made it difficult to be further modulated by tumor-conditioned supernatants (right panel). We did not test the other VEGF receptors and are planning to conduct those analyses soon. Other endothelial cell lines will also be tested similarly. Even though it might not affect NRP1 levels, it is possible that there will be differential angiogenic/oncogenic signaling. Here, we utilized an *in vitro* endothelial cell tube formation assay to evaluate the angiogenesis induction. The supernatants from KC cell cultures dramatically induced tube formation in 2H11 cells (Figure 7B), which was suppressed by blocking NRP1 activity or neutralizing VEGF (Figure 7C).

Figure 1: MUC1 up-regulates NRP1 expression in pancreatic cancer cells. A) CFPAC, HPAFII, and HPAC express moderate/high levels of MUC1. These MUC1-hi cells all express moderate to high levels of NRP1. Capan2, Panc1, Capan1, HS766T, and Miapaca2 cells have low/intermediate levels of MUC1. Other than Panc1, these low MUC1 cells also express low levels of NRP1. **B)** When BxPC3 and Panc02 cells were stably transfected with full length MUC1, NRP1 expression was substantially increased. **C)** Similarly, when MUC1 was down regulated in HPAC, CFPAC and HPAFII cells using siRNA, NRP1 levels were significantly downregulated. B-actin served as control for equal loading of protein.

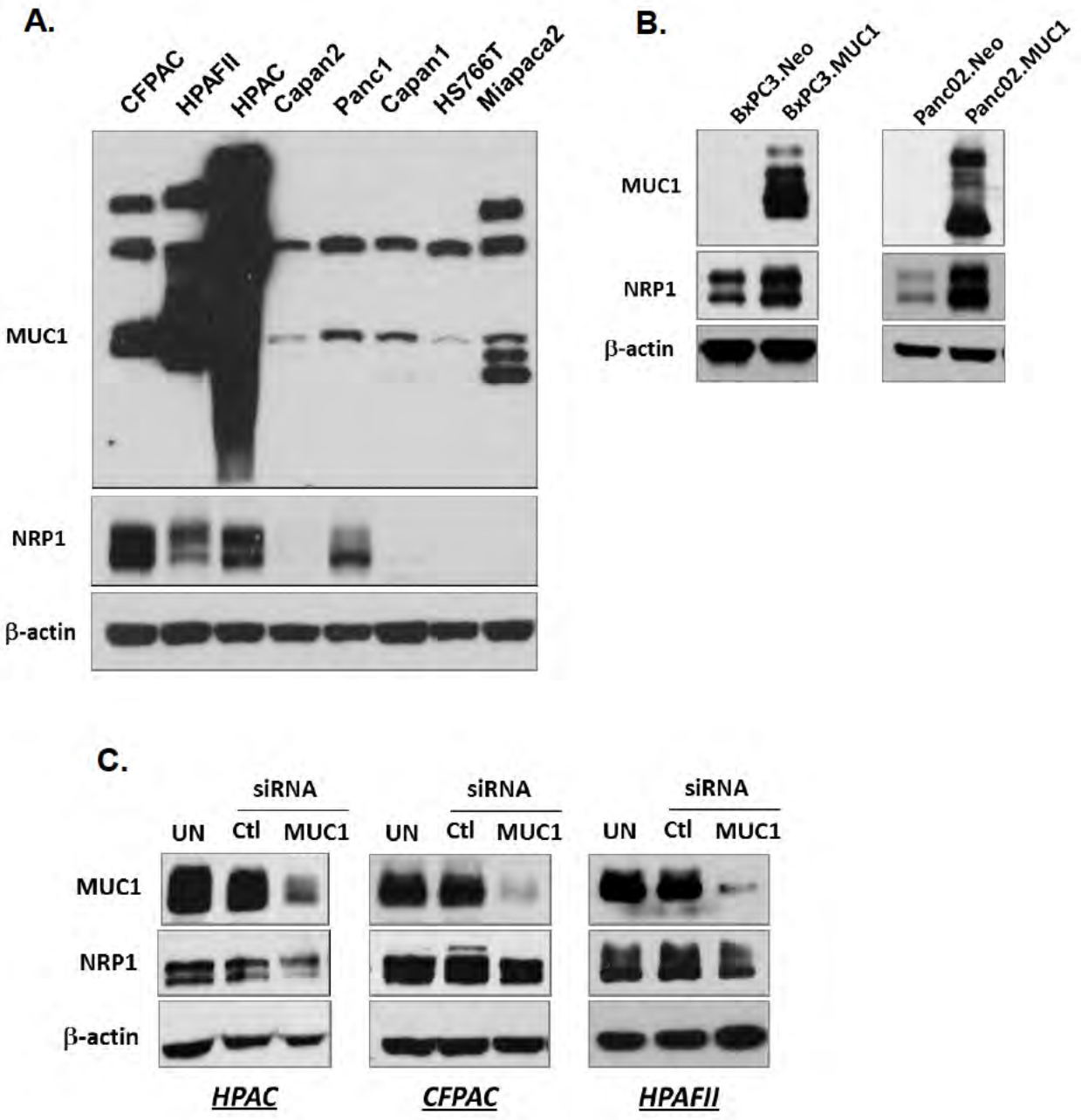


Figure 2: Microarray profile for selected gene expression in KC versus KCKO in vitro. RNA from KC and KCKO cells were extracted and run for gene microarray. Selected genes expression out of pre-chosen 323 genes was shown. Those 323 genes were pre-chosen based on that fold change of gene expression in KC versus KCKO is ≥3, or ≤ -4.

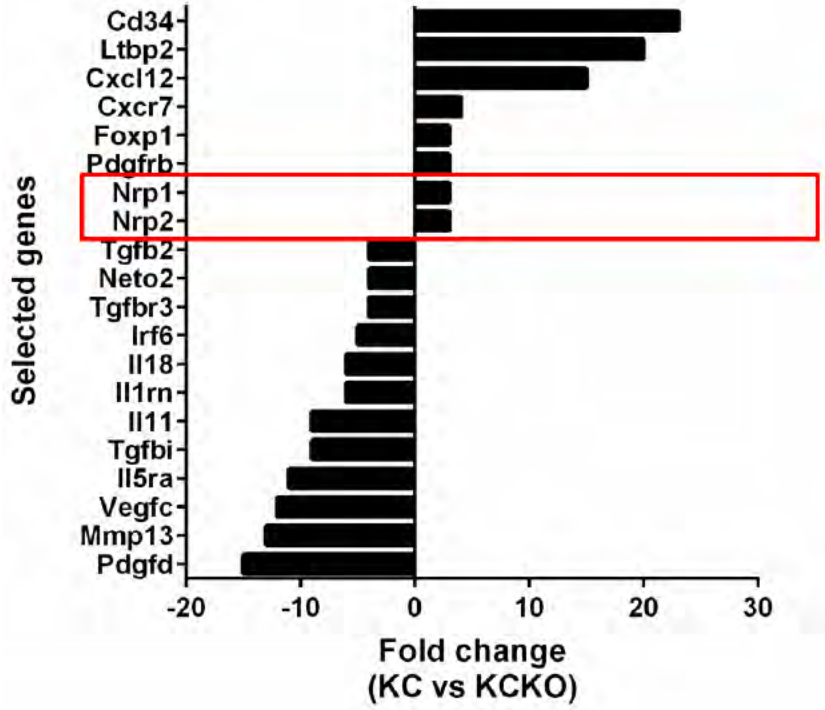


Figure 3: Higher Muc1 expression is associated with higher NRP1 level in spontaneously arising mouse PDA cells. A) KC cells are positive for MUC1 and express higher NRP1 *in vitro*, determined by flow cytometry analysis. **B)** The expression of MUC1, NRP1, and VEGFR2 are confirmed in cell lysates by Western Blot.

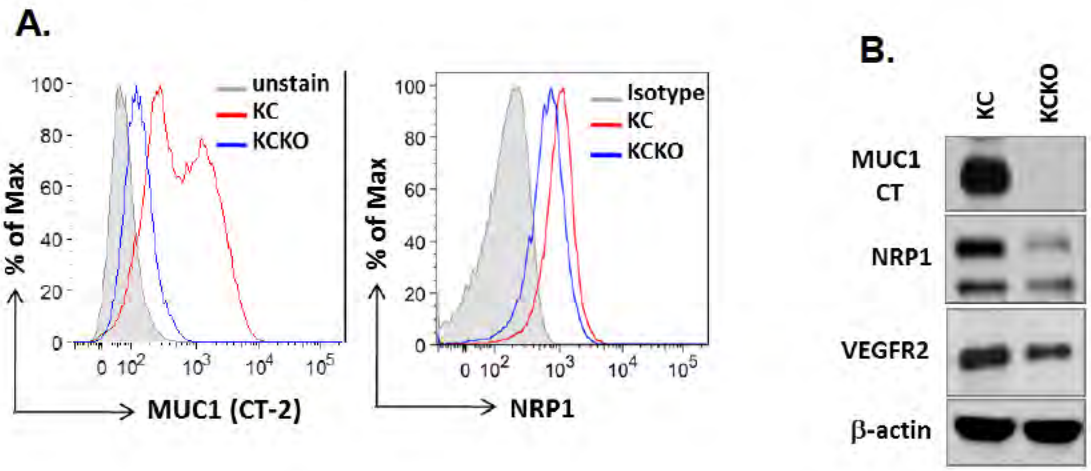


Figure 4: VEGF signaling is not required for KC or KCKO cell proliferation but may be critical for cell survival. A) KC cells have higher endogenous level of phospho-Erk and respond better to VEGF stimulation. **B)** KC and KCKO cells have similar proliferation rate (Left panel), which is not significantly changed by VEGF stimulation or NRP1 blockade (Right panel). **C)** KC cells survive better in response to serum starvation.

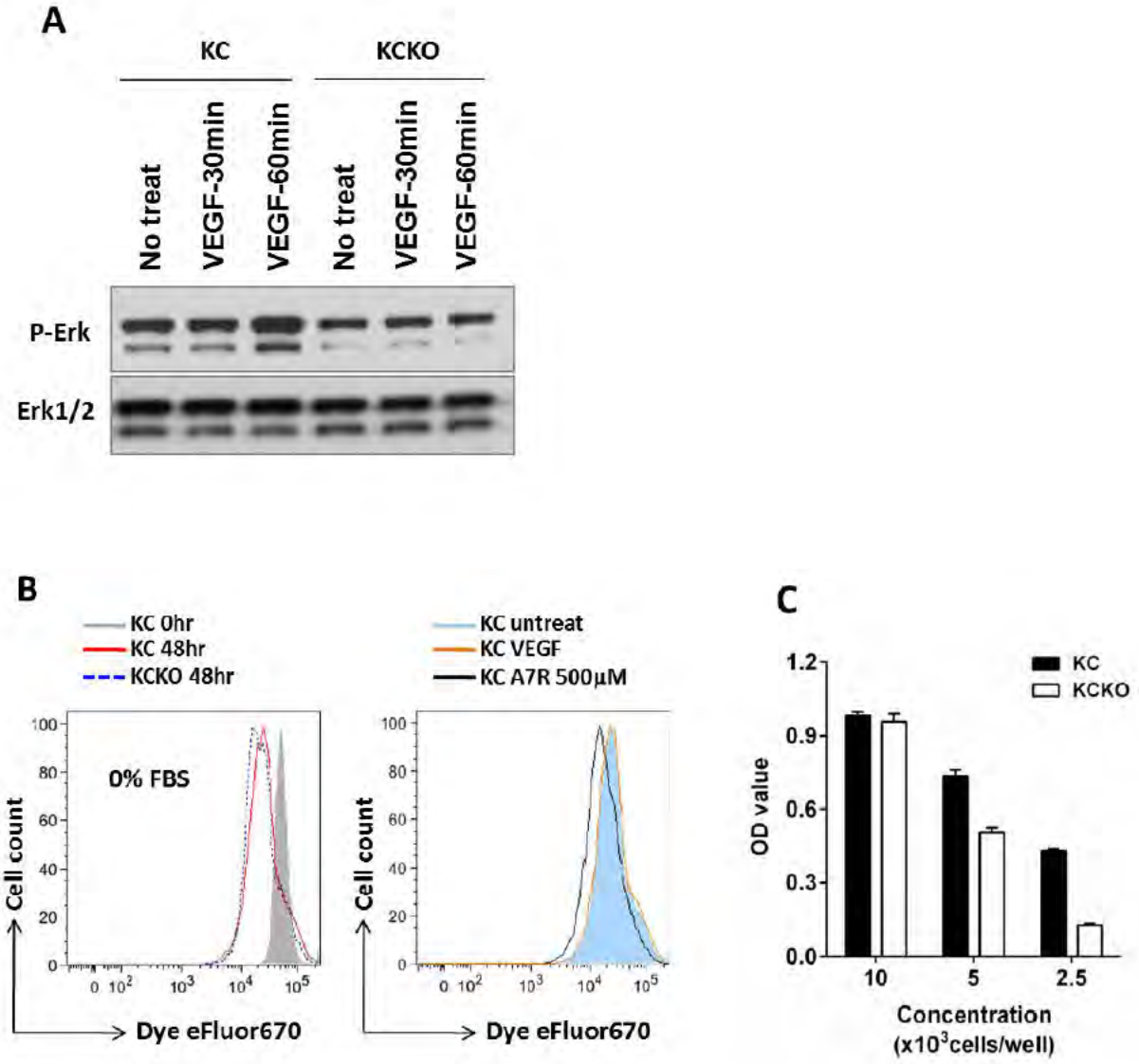


Figure 5: MUC1 enhances cell migration *in vitro*. Cells are plated and scratched. The closure of gap was monitored in **A)** KCKO versus KC and **B)** BxPC3.Neo versus BxPC3.MUC1.

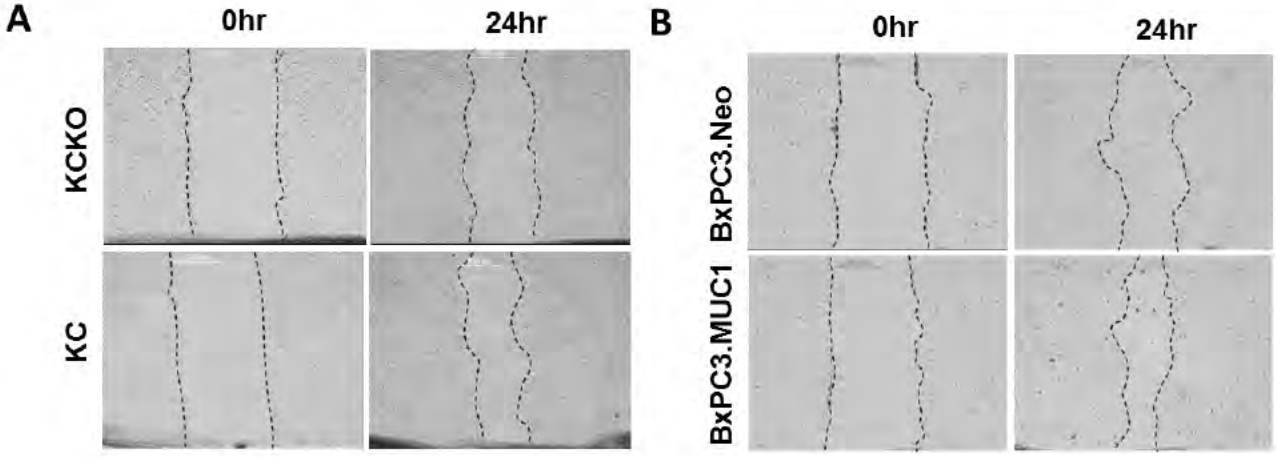


Figure 6: Blockade of NRP1 signaling decreases VEGF production by KC cells. A) KC cells produce more VEGF. **B)** NRP1 antagonist A7R does not significantly affect KC cell viability. **C)** A7R decreases VEGF secretion from KC cells.

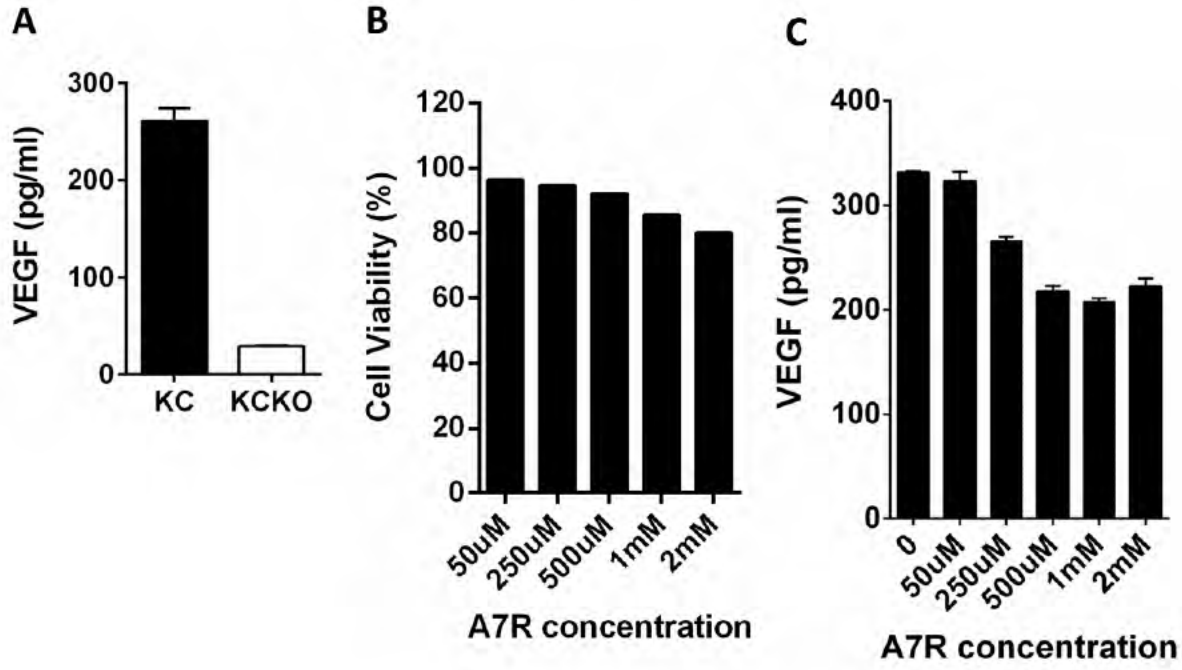
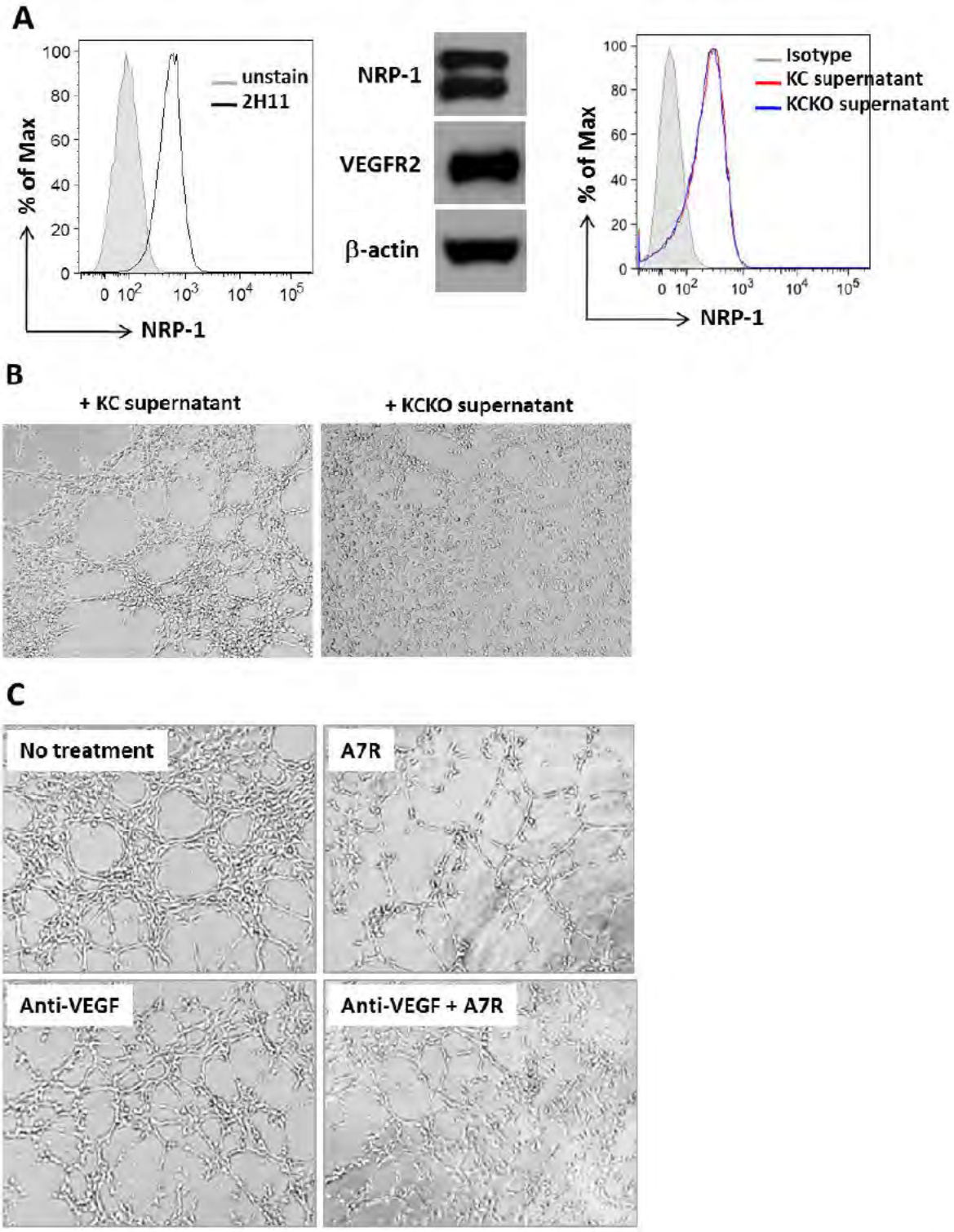


Figure 7: KC culture supernatant promotes tube formations in 2H11 endothelial cells and can be reversed by blocking VEGF signaling. A) 2H11 cells express NRP1 and VEGFR2, determined by flow cytometry (left panel) and Western Blot (middle panel). The NRP1 level is not changed by tumor conditioned medium (right panel). **B)** Tumor-derived conditioned medium from KC cell culture promotes more tube formation in 2H11 cells. **C)** The tube formation induced by KC culture medium can be reversed by NRP1 antagonism and VEGF neutralization.



Task 2:

To determine if MUC1 up-regulates NRP1 and creates a pro-angiogenic niche *in vivo* (0-22 months). For Task 2, we will use our mouse models of pancreatic cancer to determine if MUC1-expressing pancreatic tumors have enhanced intra-tumoral levels of NRP1 and angiogenesis.

KC and KCKO cells were subcutaneously injected into mouse to evaluate the activation of VEGFR2 signaling and pathways that are associated with angiogenesis. VEGFR2, the major positive signal transducer for both physiological and pathological angiogenesis is selectively expressed on vascular endothelial cells. The binding of VEGF to its receptors induces dimerization and subsequent receptor phosphorylation, which then leads to the activation of several intracellular downstream signaling pathways promoting angiogenesis [3]. Thus we looked at the levels of VEGFR2 phosphorylation in vivo in KC and KCKO tumors. Data were summarized as Figure 8. It was of great interest to demonstrate that not only were the levels of NRP1 and VEGFR2 significantly lower in the KCKO tumors, the phosphorylation at tyrosine sites of 1175, and 996 were significantly low (Figure 8), which is of course because the receptor level itself was low. Meanwhile, the higher levels of N-Cadherin and Vimentin and lower level of E-Cadherin were observed in KC tumors (Figure 8), which favor the EMT transition [4]. Together, this data suggested that in KCKO tumors, lack of Muc1 regulated NRP1 and VEGFR2 and thereby downregulated the angiogenic signaling. This is significant since NRP1 binds VEGF-A165 and only when co-expressed with VEGFR2, it enhances the binding of VEGF-A165 to VEGFR-2 by 4- to 6-fold and results in sustained vascular permeability, inflammation, and endothelial cell migration. The question still remains whether the low receptors are due to low endothelial cells and low vessels, or due to the tumor cells themselves as NRP1 and VEGFR are expressed on both the epithelial and the endothelial cells.

To further demonstrated that MUC1 up-regulates NRP1 and creates a pro-angiogenic niche in vivo, we did tissue immunohistochemistry staining for the angiogenesis-related proteins. In Figure 9, data showed that expression of NRP1, VEGF, CD31, and proliferating cell nuclear antigen (PCNA) were higher in the spontaneously arising KC tumors than those in Muc1 null KCKO tumors. This data strongly suggests that there is more onset of angiogenesis when Muc1 is present. Currently, we are breeding back and expanding those transgenic mice. In the coming year, we will address the remaining questions in those mice.

Based on the above findings and before we started the MUC1-specific tumor target therapy, we first validated the activity of NRP1 antagonist A7R in KC tumor-bearing mice. KC cells were subcutaneously injected into immune-competent C57BL/6 mice and after 4-5 days after cell inoculation, those mice were s.c. treated with A7R, 3 times a week. The growth of KC tumor was significantly reduced over the time (Figure 10A). Further, BxPC3.MUC1 tumor bearing mice were also treated with the NRP1 blocking peptide A7R. Two weeks after cell injection, we randomized groups and started therapy with A7R for 5 weeks, PBS served as the vehicle control. Mice bearing BxPC3.MUC1 tumors responded well to the mono-therapy with significantly lower tumor burden between treated and untreated mice and with 4 out of 7 mice showing a complete response (Figure 10B). Mechanistically, Western blot data from treated KC tumors further confirmed the blocking activity of A7R on the NRP1 and VEGFR2 activities (Figure 10C).

Figure 8: MUC1 enhances VEGF signaling and promotes EMT. The VEGFR2 activation and EMT switch are assessed in tumor lysates from the respective tumor bearing mice. KC and KCKO cells are subcutaneously injected into C57BL/6 mice. Twenty-six days after cell injection, tumors are retrieved and the indicated proteins in lysates are analyzed by Western Blot.

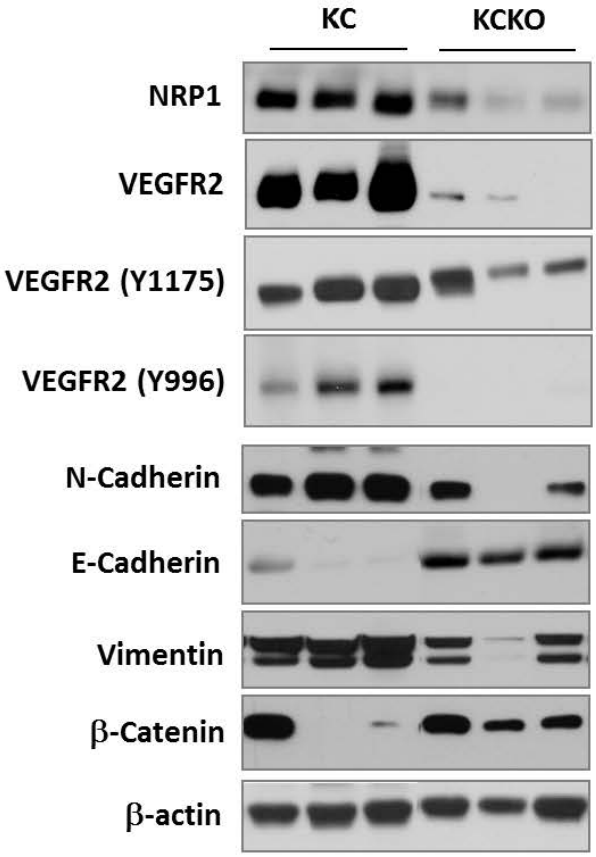


Figure 9: Higher expression of angiogenesis-associated proteins in spontaneously developed KC compared to KCKO tumors. Representative images of immunohistochemistry staining (IHC) for the angiogenesis-associated proteins.

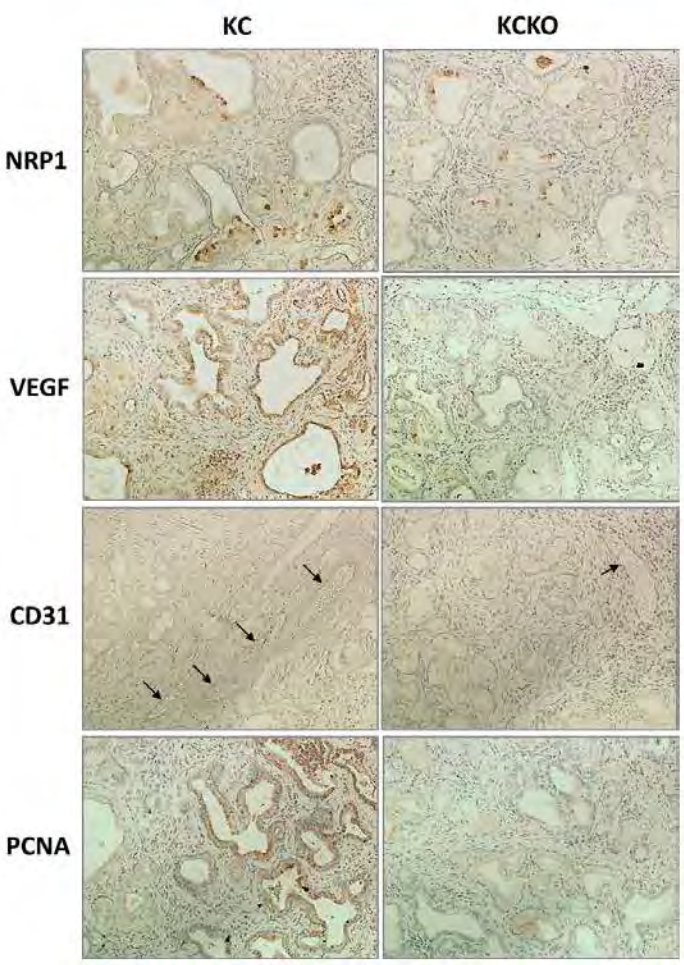
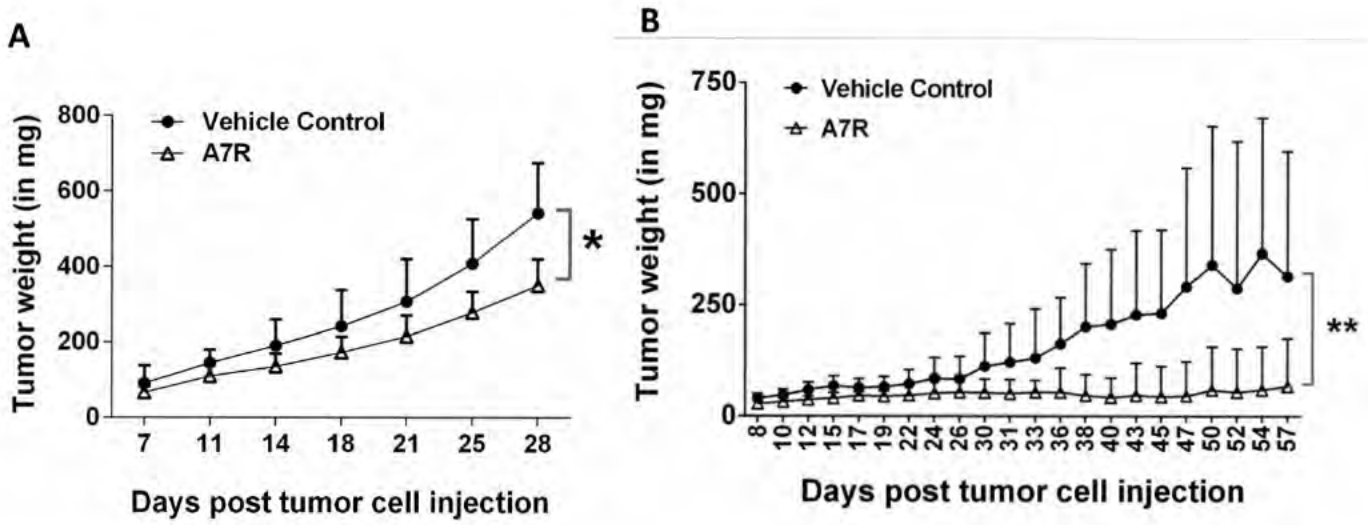
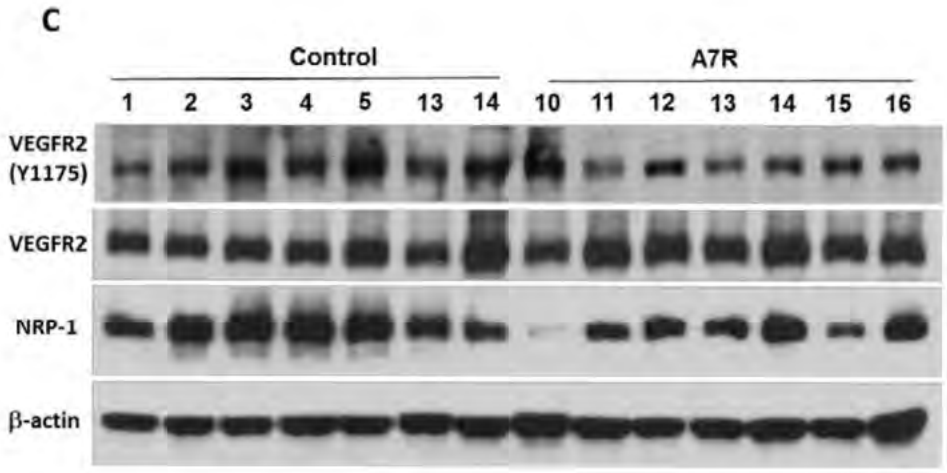


Figure 10: Blockade of NRP1 signaling attenuates MUC1hi tumor growth in vivo. A) A7R moderately attenuates KC tumor growth in C57BL/6 mice. **B)** A7R prevents BxPC3.MUC1 tumor growth in nude mice. **C)** A7R treatment in vivo reduces VEGFR2 phosphorylation as well as NRP1 level.





Task 3:

To directly target angiogenesis within the tumor microenvironment by using TAB 004 conjugated to an inhibitory peptide that blocks VEGF-NPR1 interaction (12-36 months). In this aim, we will attempt targeted drug delivery using an antibody specific for tumor-associated MUC1 (TAB 004) conjugated to a peptide inhibitor of VEGF-NRP1 binding.

With regard to targeted drug delivery using the TAB 004 MUC1 monoclonal antibody, we first showed that TAB 004 when injected intraperitoneally and intravenously specifically reaches the tumor within 24hours (Figure 11). With iv injection, we observed some reaching the spleen. Therefore, for our future experiments, we selected intraperitoneal injections. Second, we showed by in vitro confocal microscopy that TAB 004 was internalized into KCM cells through endocytosis (Figure 12). Thus, we have shown that the blocking peptide is effective in vivo and that targeting antibody internalizes in the cells and reaches the tumor bed in vivo. In addition, we show by live imaging that TAB004 localizes specifically to the pancreas tumor in the KCM mice as early as 6-8 weeks of age and since we have conjugated the TAB004 to ICG, we are able to monitor tumor progression in these spontaneously arising tumor in the pancreas. This will also enable us to monitor the effectiveness of the drug conjugate over time without euthanizing the KCM mice. Figure 13 shows proof of concept that orthotopic injection of KCM-luc tumors can be visualized with the IVIS system and that the TAB-ICG localizes specifically to the tumor (Figure 13). In Figure 14 shows that indeed the TAB004 is in the tumor and is retained there for up to 4 days. Further we show in the sponateous KCM model that TAB004-ICG localizes to the tumor and can be visualized and progression monitored using the IVIS system (Figure 15).

We have now treated the KCM mice with the TAB004-NRP1 inhibitor and are monitoring the progression of the tumor in these KCM mice. These exerimentals are surrently ongoing as these triple transgenic KCM mice can be monitored for up to 4 months.

Figure 11: Localization of TAB004 in mice bearing the MUC1+ve tumor. Mice are injected with biotin-TAB004 (50ugs/mouse) via the ip, it, and iv route. After 24hrs, mice are euthanized and TAB004 binding is detected by IHC probing with streptavidin-HRP. Brown staining indicates MUC1 expression.

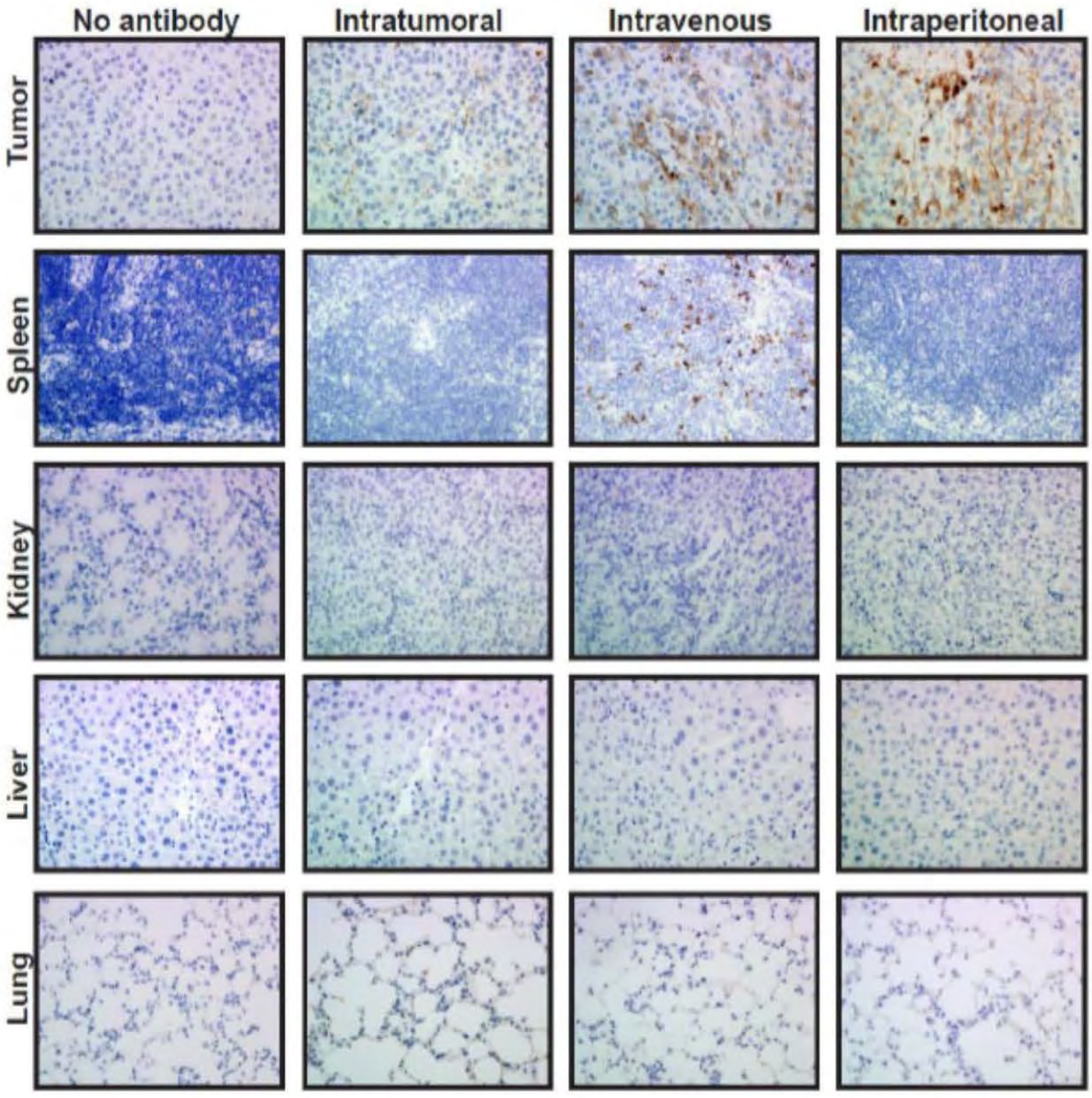


Figure 12: TAB004 binds MUC1 and get internalized in human MUC1-expressing KCM cells. KCM cells are plated on chamber tissue culture slides. Cell surface is labeled with Cell Light Plasma Membrane-GFP (Green), Lysotracker Deep Red (Lysozyme organelles, Red), and TAB004 (Yellow), followed by fixation with ProLong Gold Antifade-DAPI and image with confocal microscopy.

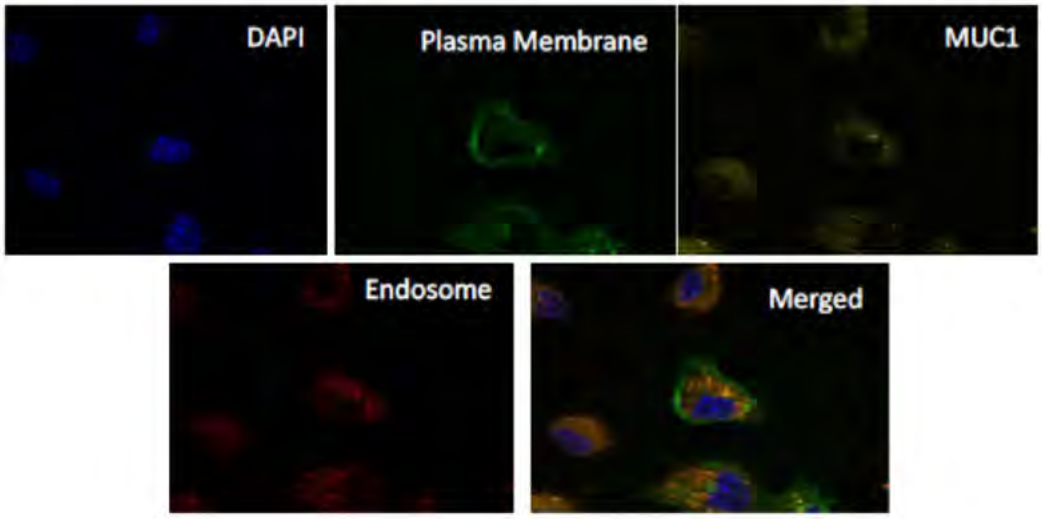


Figure 13: Lively tracking of TAB004 against MUC1-positive tumor in vivo. Luciferase-expressing KCM cells are orthotopically injected into pancreas of C57BL/6 mice. After 1-2 weeks, mice are retro-orbitally injected with TAB004-ICG. The signal of luciferase and TAB004-ICG are detected by IVIS imaging system.

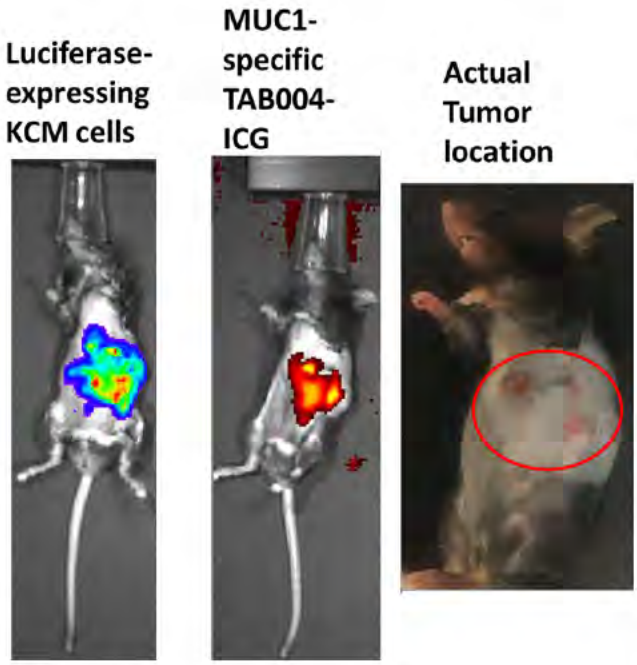
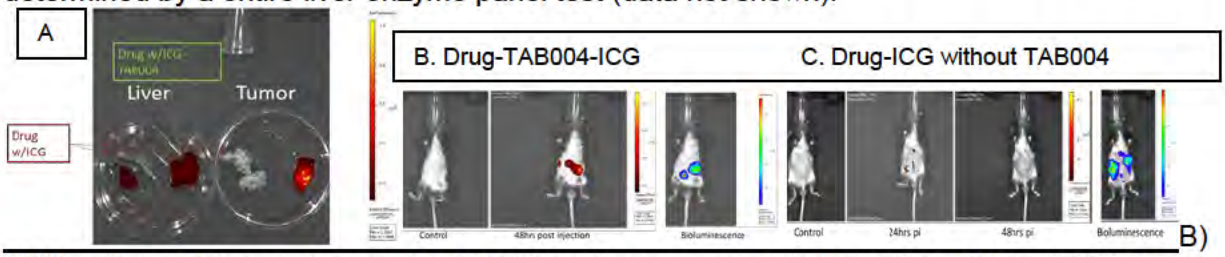


Figure 14: *Ex vivo* imaging of Drug w/ICG and Drug w/ICG-TAB004: A) Only if the drug is conjugated to TAB004 does it reach the orthotopic pancreas KCM tumor. Drug by itself fails to reach the tumor. There is some localization in the liver but this did not affect the liver function as determined by a entire liver enzyme panel test (data not shown).



B) KCM orthotopic tumor as visualized by bioluminescence and localization of drug-ICG into the tumor as visualized by the red ICG. C) Note that mice treated with drug-ICG without TAB004 conjugated does not reach the tumor even though there is are two tumors as visiaulize by the bioluminescence.

Figure 15. TAB004-ICG can be used to monitor tumor progression in the spontaneous KCM mice. As the tumors progress, there is increasing TAB004-ICG localizing to the sponatenoeus tumor. N=4mice.

Key Research Accomplishments

- MUC1 in pancreatic cancer cells regulate levels of NRP1, VEGFR and angiogenic signaling
- VEGFR, NRP1 and phosphorylation of VEGFR2 tyrosines are reduced in MUC1-ve tumors
- MUC1+ve PC cells autocrinely regulate their own VEGF production and survival
- MUC1+ve PC cells promote endothelial cell tube formation in a NRP1-dependent fashion
- MUC1 up-regulates NRP1 and creates a pro-angiogenic niche in vivo
- MUC1+ve tumors respond to NRP1 blocking peptide but MUC1-ve cells do not. This suggests that that MUC1 could be a companion diagnostic for anti-angiogenic therapy targeting NRP1.
- MUC1 antibody (TAB 004) internalizes in the MUC1+ve tumor cells through endocytosis suggesting that the drug will be internalized when conjugated to TAB 004.
- Established the four color confocal images for plasma membrane, lysosomes, MUC1, and DAPI
- TAB 004 localizes to the tumor when injected intraperitoneal and intravenous within 24hours
- Live imaging of tumor bearing mice to verify the MUC1-specific tumor targeting by TAB004, which will benefit the tracking of tumor growth in live animals over the study period.

Conclusion

In conclusion, we show that NRP1 may be an excellent target for treating MUC1+ve PDA but not MUC1-ve PDA. It is doubtful that a monotherapy with NRP1 blockade will work and therefore using the TAB 004-conjugated to the drug may show promise due to ADCC caused by the antibody and thereby making the tumors more vulnerable to NRP1 blockade. In the long term, combination therapy with standard of care drug and NRP1 blockade conjugated to TAB 004 or two drugs packaged in nanoparticles and conjugated to the antibody might be highly efficacious for patients with pancreatic cancer.

Publications, Abstracts, and Presentations

Ru Zhou, Jennifer Curry, Priyanka Grover, Lopamudra Das Roy, TinChung Leung, and Pinku Mukherjee. **MUC1 enhances neuropilin-1 signaling in pancreatic ductal adenocarcinoma.** AACR Annual Meeting 2014; April 5-9, 2014; San Diego, CA

Ru Zhou, Jennifer M Curry, Lopamudra Das Roy, Priyanka Grover, Jamil Haider, Laura J. Moore, Shu-ta Wu, Anishaa Kamesh, Mahboubeh Yazdanifar, TinChung Leung, Pinku Mukherjee
A Novel Association of Neuropilin-1 and MUC1 in Pancreatic Ductal Adenocarcinoma: Role in induction of VEGF signaling and angiogenesis. *Submitted to Oncogene*

Inventions, Patents and Licenses

None

Reportable Outcomes

- Two manuscripts are in preparation, 1) The effect of NRP1-VEGF signaling axis on MUC1 +ve epithelial tumor cells and 2) The effect of NRP1-VEGF signaling axis on endothelial cells within MUC1+ve tumors.
- Research work has been presented as abstract in 2014 AACR annual meeting.
- Research Associate hired for the project, Graduate students are working on parts of the project and in the future will get publications and degrees out of this work.
- Patient pancreatic cancer serum and tissue collected for future analysis.
- KC, KCM, and KCKO cells are further characterized due to this project
- Development of a novel antibody-anti-angiogenic drug conjugate that can be used in immune competent mouse model of spontaneous PDA and can be potentially translated to human clinical trials.

Other Achievements

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Appendices

NONE